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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,419	08/16/2000	Hartwig Schroder	48792	3392

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 01/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/622,419	SCHRODER, HARTWIG	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE f this communication appears on th c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Non-final

1. Applicants petition filed under 37 CFR 1.144 to the finality of the Lack of Unity, dated December 03, 2003, is acknowledged. The petition is being has been reviewed and the decision communicated to the Applicants in the letter mailed 5.5.2004. The key points of the decision are reproduced as follows:

DECISION

Applicant's petition is DENIED for the reasons recited in the decision. Any request for consideration must be filed within two (2) months of the mailing date of this decision. Upon reconsideration, the finality of the office action dated October 7, 2003 will be withdrawn. The application will be forwarded to the Examiner for the preparation of a Supplemental Office action consistent with this decision including: the applicability of references cited in the PCT/EP99/01052 Search Report particularly Patent Abstract of Japan Vol. 098, No. 001 (Jan. 30, 1998); and b. reconsideration of the indication of allowable subject matter concerning SEQ ID No 1 and SEQ ID No 3 and if deemed allowable, reasons for allowance provided.

2. The finality of the office action dated October 7, 2003 has been withdrawn in view of the applicability of references cited in the PCT/EP99/01052 Search Report particularly Patent Abstract of Japan Vol. 098, No. 001 (Jan. 30, 1998) and as explained in the petition decision; and after waiting the required time period.

3. Claims 1 & 3-6 [Group I] are pending and under consideration in this examination.

4. Claim 15 is not being considered along with the processes claims because of the prior Lack of Unity of Invention, and according to which - Claims 1, 3-6 & 12 (in-part) drawn to a process of producing biotin using a host organism transformed with the gene sequence of **SEQ ID NO : 1** [SAM-synthase] and the biotin synthesis gene of **SEQ ID NO : 3** [bioS1] were under consideration. Claim 15 recites a process for producing biotin wherein SAM synthase and at least one biotin biosynthesis gene selected from the group consisting of O-acetyl serine sulfohydrolase A, O acetyl serine sulfohydrolase B, beta-cystathionase, nifS.....

The new group consisting of O-acetyl serine sulfohydrolase A, O acetyl serine sulfohydrolase B, beta-cystathionase, nifS, is a new addition. Claim 15, therefore will not be considered, since the Newly submitted claim 15 is directed to an invention that is independent or distinct from the invention originally claimed and for which the Applicants have received an action on the merits.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 15 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. **Claims 1 & 3-6 (drawn nly to SEQ ID N s. 1 & 3) are und r consideration in this examination.** Please make a note in amending claims.

REMINDER !!!!!

6. Applicants are reminded again that SEQ ID NO : 5 & 7 or similarly unrelated language is not under consideration, and that subject matter of inventions of Groups not under consideration be deleted, for example, from current claims 1 & 3-6.

7. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s). Moreover, no new arguments have been presented, apart from the change of homology from 50-100% to 80-100% in the amended claims

8. ***Enablement Rejection***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, does not reasonably provide enablement for using any of the functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 (claims 1, 3-6 & 12), or wherein the deduced amino acid sequences of the gene sequences of SEQ ID NO : 1 & 3 have a homology of 80-100% and enable increased biotin production, or

express the variously modified sequences in various host organisms irrespective of the host being capable of producing biotin, or its expression in regulation-defective biotin mutants (claims 3-6), either alone or in shared vector or on separate vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have described a single construct of co-expression of the combination of metk (SEQ ID NO : 1) and bioS1 (SEQ ID NO : 3) from *Escherichia coli* (see pages 15 of the instant specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims are so broad as to encompass a process of using a modified gene of SEQ ID Nos. 1 & 3 for biotin production, wherein the sequences are modified by any extent and includes deletion, substitution or insertion (functional variants or analogs); prokaryotic or eukaryotic homologs from bacteria, fungi, plant, animal or human (functional analogues)and truncated sequences thereof; or derivatives (claims 1, 3-6), or wherein the sequences are modified to having sequence homologies of 80-100% (claim 2) (*see* Specification, page 5, lines 22-47 for Applicants definitions). Applicants have neither disclosed nor described, or exemplified the numerous proposed modifications encompassed by the claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of SAM-synthase and/or biotin biosynthesis genes broadly encompassed by the process claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequences of SEQ ID Nos. 1 & 3 from which amino acid sequences can be deduced.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of SEQ ID Nos. 1 & 3 or that ranging in homology from 50-100% identity to the encoded amino acid sequences, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of enzyme to modification and extent of such tolerance; □ a rational and predictable scheme for modifying any enzyme residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method or process of using said enzyme(s) with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of process of using such enzymes (SAM-synthase & biotin biosynthesis enzyme) having the desired biological characteristics or its co-expression into any host which may include a host cell not capable of biotin production, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and

undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Prior Applicants' Arguments :

Applicants citing specification page 5, lines 23-29, argue that the specification clearly indicate that a number of other enzymes are known to have the ability to assume the enzymatic activity of bioS1, bioS2 & bioS3. Given the broad range of genes known in the art to be suitable substitutes, the ability of one skill in the art to recognize and use functional equivalents is relatively high - accordingly the homology range now recited in claim 1 is enabled.

In response, first it is again emphasized that bioS1 or SEQ ID NO : 3 & SEQ ID NO : 1 is under consideration. Further, it is not clear what broad range of genes are known as suitable substitutes. What substitutes are functional equivalents ? And how Applicants have arrived at the conclusion that the homology range of 80-100% is now enabled ? Clearly the specification provides no guidance to any enablement issues or written description issues as indicated by the Applicants. Applicants have clearly, either in-part or wholly not addressed many of the issues pertaining to enablement or written description rejections presented in the prior Office Action.

9. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1 & 3-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such

a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1 & 3-6 recite □functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3. However, description to any such functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 is lacking (claims 1 & 3-6).

Further claim 1, recite 80-100% homology to the deduced amino acid sequences of SEQ ID Nos. 1 & 3. The specification, however, only provides a process for using a single representative species of a combination of full length gene sequences from *E. coli* of SEQ ID Nos. 1 & 3 for biotin production. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species or modify the enzyme by substitution, insertion or deletion (analogues, variants or derivatives) or make a polypeptide 80-100 % identical to the encoded amino acid sequences deduced from the gene sequences of SEQ ID Nos. 1 & 3 and have the desired biological activities for biotin production. The specification also fails to describe additional representative species of these combinations by way of modifications such as that claimed by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Further, description of expressing SEQ ID Nos. 1 & 3 into any prokaryotic or eukaryotic host organism either

alone, or on shared vector or on separate vectors is also lacking. Given this lack of additional representative species, such as the proposed modifications of SEQ ID Nos. 1 & 3 and still retain functional characteristics of a process for producing biotin, or various host cells or the expression into single or shared vector, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicants Arguments : No specific or new arguments presented.

10. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 &3 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakahama Kazuo [Patent abstract of Japan (EPO), publication number 09224690 (2/9/97) (Applicants' IDS)]. Nakahama Kazuo teaches a method of producing biotin, an important vitamin, by culturing a microorganism [*E. coli*] transformed with a SAM synthase gene (example SEQ ID NO: 1) and the biotin operon which must include a biosynthetic gene representative of functional variants, analogue or derivative" of any of SEQ ID No 3, 5 or 7. The claims are written so broadly as to be anticipated by the reference.

11. Rejoinder: The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

In this case, Applicants had elected to prosecute the process claims of Group I [claims 1 & 3-6). As indicated in the rejoinder notice, process claims that depend from or otherwise include all the limitations of the patentable product claims are rejoined, a situation in which the product claims are under examination. However, in the instant case the process claims are under examination and therefore, the product claims of Group IV (claims 7-11 & 14), drawn to gene construct comprising SEQ ID NO: 1 and SEQ ID NO: 3[BioS1], is not subject to the rejoinder notice. Any request for such a rejoinder cannot be considered at this time because the claims do not meet the criteria for patentability.

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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